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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
|-----------------|-------------|----------------------|---------------------|------------------|

10/566,822

01/31/2006

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BY0029YP

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210 7590 01/28/2010
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EXAMINER

SCHNIZER, RICHARD A

ART UNIT

PAPER NUMBER

1635

MAIL DATE

DELIVERY MODE

01/28/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|--------------------------------------|--------------------------------------|--|
| Office Action Summary | Application No. 10/566,822 | Applicant(s) KOTANI ET AL. | |
| | Examiner Richard Schnizer | Art Unit 1635 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 December 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 8-11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 31 January 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/10/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

An amendment was received on 12/10/09.

Claims 8-11 remain pending and are under consideration.

In the response filed 7/8/09, Applicant elected group 6 without traverse, drawn to methods for treating obesity using an siRNA set forth in instant SEQ ID NOS: 9 and 10.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 8-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 10 and 11 were amended to be drawn to methods requiring RNAi molecules "synthesized from a DNA sequence pair", selected from the group consisting of a series pairs of SEQ ID NOS comprising elected SEQ ID NOS: 9 and 10. The claims as originally filed referred to siRNA consisting of SEQ ID NOS: 9 and 10. The specification at pages 31 and 32 indicates that SEQ ID NO: 9 is a sense sequence, and SEQ ID NO: 10 is an antisense sequence. Nowhere in the application as filed does the

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specification refer to any RNAi molecule synthesized from a DNA sequence pair consisting of SEQ ID NOS: 9 and 10. As a result, the claims as amended recite new matter. Note that claims 8 and 9 are included in this rejection because they embrace amended claims 10 and 11.

Enablement

Claims 8-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The elected invention is a method of treating obesity by inhibiting fatty acid synthesis in an individual comprising administering to the individual an RNAi molecule synthesized from the DNA sequence pair SEQ ID NO: 9 and SEQ ID NO: 10.

As discussed above, the specification as filed discloses that SEQ ID NOS: 9 and 10 constitute an siRNA. As discussed in the Action of 9/1/09, this is not possible because SEQ ID NOS: 9 and 10 are not RNA oligonucleotides, they are DNA oligonucleotides.

In the response filed 12/10/09, Applicant explains that the disclosed DNA oligonucleotides were used to generate siRNA molecules using an Ambion Inc. silencer siRNA kit. Briefly, this requires separately annealing SEQ ID NOS: 9 and 10 to T7 promoter primers and extending each primer with Klenow fragment of DNA polymerase

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to prepare templates for RNA transcription. RNA is then transcribed from each template, and the resulting transcripts are annealed to create a dsRNA duplex with 5' single stranded regions, a central duplex region, and 3' terminal UU dinucleotides. The 5' single stranded regions are removed by treatment with a single strand specific RNA ribonuclease to yield the desired siRNA.

Because SEQ ID NOS: 9 and 10 cannot form an siRNA unless they are used as described in the Ambion kit used by Applicants, the information and guidance required to perform the method of the kit constitute essential guidance that is required to make the siRNAs referred to in the instant claims. Moreover, the kit comprises essential materials such as the T7 promoter primers, T7 polymerase, and nucleases, that are required in order to produce the desired siRNAs. The specification as filed does not disclose any of this guidance or any of these essential materials except by indirect reference, stating at paragraph 114 that "a silencer RNA construction kit (Ambion Inc.) was used to synthesize siRNA." The specification does not incorporate by reference any information associated with the use of the Ambion kit. 37 CFR 1.57(c) states that essential material may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. If essential material is incorporated by reference to non-patent literature, then MPEP 608.01 (p) indicates that "[p]articular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found". In such cases, Applicant may attempt to insert the

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essential material into the specification without introducing new matter. However, in this case the essential material was not incorporated by reference, and so the essential material cannot be inserted into the specification by amendment.

The specification as filed does not indicate what DNA oligonucleotides were used with the Ambion kit. Instead the specification objectively states the following:

that RNAi of Slc25a10 may be accomplished by using siRNA consisting of the nucleic acids of SEQ ID NOS: 9 and 10 (paragraph 15 on page 4);

that RNAi is preferably accomplished using siRNA consisting of the nucleic acids of SEQ ID NOS: 9 and 10 (paragraph 16 on page 5);

that the sequence of siRNA H4 consists of SEQ ID NOS: 9 (sense) and 10 (antisense) (paragraph 79 on page 23, and paragraph 115 on pages 31 and 32); and

siRNA consisting of SEQ ID NOS: 9 and 10 powerfully inhibit Slc25a10 expression (paragraph 84, page 24).

These objective statements cannot be overlooked. While the specification indicated that an Ambion silencer siRNA construction kit was used to synthesize siRNA, it never stated what materials were used in the kit, it never indicated that SEQ ID NOS: 9 and 10 served as templates for an expression construct for an siRNA, and instead it repeatedly stated that SEQ ID NOS: 9 and 10 are part of an siRNA. The Examiner agrees that those of skill in the art who were familiar with the particular Ambion kit used by Applicants probably could have determined how to use SEQ ID NOS: 9 and 10 to make siRNA useful for inhibiting Slc25a10 expression. However, it cannot be assumed that all persons of skill in the art at the time of the invention were familiar with the

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particulars of the Ambion kit. Therefore, it is not clear that those of skill in the art, who had no experience with the Ambion kit, would have appreciated that the CCTGTCTC sequence present in SEQ ID NOS: 9 and 10 was the complement of a leader sequence present in the Ambion T7 promoter primer to which said promoter primer must be annealed in order to generate desired siRNA. Accordingly, it is unclear that one of skill would have appreciated that the DNA sequences of SEQ ID NOS: 9 and 10 were intended as templates for generating expression constructs for expressing an siRNA. Furthermore, the Ambion kit is proprietary, and its contents and principle of operation could change over time at the discretion of Ambion, such that one of skill could not necessarily rely on the specification's reference to the kit as guidance as to how to make the disclosed siRNAs. Accordingly, the specification as filed does not satisfy the requirement of 35 USC 112, first paragraph that it should contain a written description of the invention in such **full**, clear, concise, **and exact** terms as to enable **any** person skilled in the art to which it pertains to make and use the invention.

Because the claims under examination in the Action of 9/1/09 were directed to an invention that was clearly non-functional, there was no need at that time to assess the state of the art of siRNA therapy as it related to enablement of the claims. The claims as amended now include an embodiment which would generate functional siRNA that could be used to down-regulate Slc25a10 mRNA such that a consideration of these issues is now appropriate.

The state of the art at the time of filing shows that RNA interference was recognized as not enabled for therapeutic purposes. (See for example, Agami et al.

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2002 Current Opinion in Chemical Biology. Vol. 6, pp. 829-834; Caplen 2003, Expert Opin. Biol. Ther. 2003, Vol. 3, pp. 575-586; and Coburn et al. 2003, Journal of Antimicrobial Chemotherapy. Vol. 51, pp. 753-756 for reviews on the progression of RNA interference in mammalian cells and the state of the art of RNA interference for therapeutic purposes).

Opalinska et al. (Nature Reviews Drug Discovery, 2002, Vol. 1, pp. 503-514) stated, “[l]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA”, and in column 2 of the same page, “[a]nother problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded.”

Caplen (2003) taught out that, “[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required

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tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system...". (pg. 581).

Coburn et al. (2003) taught that the major impediment to using RNA interference as a therapeutic is that suppression of gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example p 754, first column, last paragraph).

Zhang et al (Current Pharmaceutical Biotechnology 2004, Vol. 5, pp.1-7) reviewed the state of the art with regard to RNAi, and stated "[u]se of siRNA in mammalian cells could be just as far-reaching, with the applications extending to functional genomics and therapeutics. But various technical issues must be addressed, especially for large-scale applications. For instance, dsRNA can be delivered to *C. elegans* by feeding or soaking, but effective delivery of siRNAs to mammalian cells will not be so simple."

Thus it is abundantly clear that it was not routine prior to and after the time of the invention for those of skill in the art to perform therapy by delivery of siRNA to target cells *in vivo*, particularly by methods other than those that allow delivery directly to the target cells.

In particular regards to Applicant's *in vitro* example, often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism). For example, Agrawal et al (Mol. Med. Today 6:72-81, 2000) stated "[t]he cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*in vitro*, cellular uptake of

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antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Agrawal discussed these factors in relation to antisense, but they would also apply to dsRNA. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies").

In regards to the amount of direction provided by Applicant as to how one of skill in the art would practice the full scope of the claimed invention, guidance in the specification is limited to the suggestion of systemic administration routes, as well as intramuscular and subcutaneous routes. The specification provides no guidance as to how to obtain delivery of the siRNAs to adipose cells by any of these routes. The specification as filed does not disclose any delivery formulations or techniques that were not available in the prior art, and so does not adequately address the state of the art at the time of the invention with regard to siRNA delivery to target cells *in vivo*.

Given the recognized unpredictability in the art of nucleic acid therapeutics, one of skill would still require specific guidance to practice the claimed methods *in vivo* in any organism or any mammal, with the resultant specified biological effect of treating or obesity. However, the specification does not provide either examples or the required guidance to allow one of skill in the art to reliably and predictably obtain success using the claimed methods *in vivo*. The specification does not overcome the art recognized

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obstacles to *in vivo* RNAi, particularly in terms of specific targeting and delivery of the dsRNA to a whole organism.

In summary, the specification as filed omits critical subject matter required for the practice of the invention, and fails to meet the enablement requirement for that reason alone. In addition, the specification fails to provide adequate guidance or working examples that would be required, in view of the unpredictability of the invention as evidenced by the state of the art, to reliably achieve treatment of obesity. Thus one of skill in the art could not practice the invention without undue experimentation.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Tracy Vivlemore, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Richard Schnizer/
Primary Examiner, Art Unit 1635